REMARKS

Claims 1-17 are pending in the present application. The Examiner has maintained the rejection of claims 1-17 under 35 U.S.C. §103, as being obvious over U.S. Patent No. 5,616,568 (Pouyani, *et al.*), in view of K. Kyyrönen, *et al.*, International Journal of Pharmacetuics 80:161-169 (1992).

Applicant respectfully traverses these rejections.

Applicant urges that the Examiner has failed to make out a *prima facie* case of obviousness for these rejections. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the combination of prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.

Applicant's independent claim 1 is directed to a "microsphere comprising hyaluronan derivatized with a crosslinker at carboxyl groups of glucuronic acid sites . . .", while independent claim 8 is directed to a "method for making a functionalized hyaluronic acid microsphere . . .".

Pouyani is directed to hyaluronic acid (HA) compositions functionalized by covalent attachment of pendant hydrazido groups that have formed biocompatible gels or hydrogels. As noted in Pouyani, "The term gel is intended to mean viscous or semi-solid and jelly-like. The term hydrogels is intended to mean macromolecular networks which swell in water. They can be thought of as being composed of hydrophilic monomer units linked to form a soluble polymeric network and eventually crosslinked to form an insoluble network." (Col. 3, lines 44-51.) These gels can form "porous sheet like structures with pore sizes in the range 20-100μm." (Col. 33, lines 22-23.) Pouyani states further that these gels support the

"formation of highly porous, three-dimensional networks in the crosslinked hyaluronate" (Col. 33, lines 25-26.), and characterizes the gel as "an ordered macroporopus structure". (Col. 33, line 35.)

The Examiner conceded that Pouyani does not teach microspheres comprising functionalized hyaluronan, but then cited Kyyrönen as teaching derivative microspheres of hyaluronic acid. Although Kyyrönen does disclose films and microspheres prepared from various esters of hyaluronic acid, Kyyrönen is silent on hyaluronic acid derivatized with hydrazides, and thus does not teach or suggest "hyaluronan derivatized with . . . a dihydrazide" as recited in claim 1, or a "functionalized hyaluronic acid microsphere comprising mixing hyaluronic acid and a dihydrazide . . .", as recited in claim 8.

Further, Applicant urges that there is no motivation or suggestion in the references themselves to combine these reference teachings. First, the teachings of Pouyani regarding hydrogels and macroporous networks teach away from microspheres. As Applicant previously stated, gels and networks are diametrically opposed to microspheres. Microspheres are substantially spherical particles of microscopic dimension or roughly identical size in each of three dimensions. As taught by Applicant's disclosure, the microspheres have a diameter in the range from about 1 to about 500 μm. A matrix, gel, or macroporous structure such as that taught by Pouyani is of macroscopic size and can have different sizes in each dimension, e.g., the sheet-like structures disclosed in Example 8. Thus, microspheres are not a macroporous structure. Moreover, Applicant's microspheres further "compris[e] a component incorporated into the microsphere", as recited in claim 7. While the Pouyani's hydrogels can be carriers of agents, they cannot incorporate components in individual units as can microspheres.

Second, combining Pouyani with Kyyrönen would render Pouyani's composition unsatisfactory for its intended purpose. Pouyani's hydrogels find use in tissue engineering, where crosslinked biodegradable derivatives of hyaluronate can be produced with defined pore size that may vary according to the choice of crosslinker and mode of preparation of the crosslinker. The defined pores can provide support to cells such as keratinocytes,

chrondrocytes and osteoblasts which can adhere and subsequently grow in three dimensions for use in skin grafts, nerve repair and cartilage and bone repair. (Col. 14, lines 16-29.) However, this use of Pouyani's hydrogels would be defeated by replacing a porous gel with microspheres, which lack the porous 3-D network for supporting cell growth. Since the Examiner's proposed modification of Pouyani with Kyyrönen's microspheres would render Pouyani's gels unsatisfactory for their intended purpose, there is no suggestion or motivation to make this modification. (See MPEP 2143.01, citing In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).)

Applicant respectfully urges that the Examiner, in responding to Applicant's arguments filed on November 3, 2004, confuses pore size with microsphere size. Although, as stated in Applicant's response filed on November 3, 2004, the pore sizes of the hydrogels are of the same order of magnitude as the diameter of the microspheres, Applicant observes that pores are holes, and as such are diametrically opposed to microspheres, which are particles. Applicant urges that this difference, contrary to the Examiner's assertion, teaches away from the obviousness rejection of record.

Furthermore, point three of the Examiner's response to Applicant's arguments does not respond to Applicant's argument that Pouyani's gels and networks teach away from microspheres, and that combining Pouyani with Kyyrönen would defeat the purpose of Pouyani's invention. Point three reiterates that Pouyani teaches hyaluronic acid compositions functionalized by covalent attachment of pendant hydrazido groups that have formed biocompatible gels or hydrogels. The Examiner goes on to state that these compositions can be linked to form first a soluble network and then crosslinked to form an unsoluble network, without addressing the fact that this property of Pouyani's composition teaches away from the microspheres recited in claims 1 and 8. The Examiner also did not respond to Applicant's argument that combining the teachings of Pouyani with those of Kyyrönen to produce the microspheres recited in claims 1 and 8 would defeat the purpose of Pouyani's invention.

Accordingly, Applicant urges that a *prima facie* case of obviousness of claims 1 and 8 over Pouyani and Kyyrönen cannot be maintained. Reconsideration and withdrawal of these rejections are respectfully requested.

Dependent claims 2-7 and 9-17 depend ultimately from either claim 1 or claim 8, and are thus patentable for at least the same reasons as claims 1 and 8. Reconsideration and withdrawal of these rejections are respectfully requested.

CONCLUSION

Applicant urges that claims 1-17 are in condition for allowance for at least the reasons stated. Early and favorable action on this case is respectfully requested.

Respectfully submitted,

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